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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/368,630	08/05/1999	DAVID M. CENTER	12875	5759

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	18

DATE MAILED: 06/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/368,630	CENTER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 15 March 2002 (Paper No. 17) has been entered in full. Claims 2-33 and 35 are amended and claims 1, 34, and 36-42 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2-33 and 35 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 3-4 of the previous Office Action (Paper No. 16,15 August 2001) are *withdrawn* in view of the amended abstract and specification (Paper No. 17, 15 March 2002).

2. The objections to claims 2, 6-7, 9, 14-15, 17, 19, 22-23, 25, 27, 33, and 35 at pg 4-5 of the previous Office Action (Paper No. 16, 15 August 2001) are *withdrawn* in view of the amended claims (Paper No. 17, 15 March 2002).

3. The rejection of claims 1-33, 35, and 40-41 under 35 U.S.C. § 101 at pg 5 of the previous Office Action (Paper No. 16, 15 August 2001) are *withdrawn* in view of the amended and cancelled claims (Paper No. 17, 15 March 2002).

4. The rejection of claims 1-33, 35, and 40-41 under 35 U.S.C. § 112, second paragraph at pg 8-10 of the previous Office Action (Paper No. 16, 15 August 2001) is *withdrawn in part* in view of the cancelled claims and Applicant's persuasive arguments (Paper No. 17, 15 March 2002). Please see section on 35 U.S.C. 112, second paragraph, below.

5. The rejection of claims 1, 33, 35, and 40-41 under 35 U.S.C. 102 at pg 10 of the previous Office Action (Paper No. 16, 15 August 2001) is *withdrawn* in view of the amended and cancelled claims (Paper No. 17, 15 March 2002).

Claim Rejections - 35 USC § 112

6. Claims 1-33 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated IL-16 antagonist peptide consisting of the amino acid sequence of SEQ ID NOs: 2, 5, 6, 17, and 24 and a composition comprising an isolated IL-16 antagonist peptide consisting of the amino acid sequence of SEQ ID NOs: 2, 5, 6, 17, and 24 and a carrier, does not reasonably provide enablement for an IL-16 antagonist peptide, an IL-16 antagonist, an IL-16 antagonist peptide consisting of the amino acid sequence of SEQ ID NOs: 3-4, 9-11, 13-16, 18-23, 25-32, and 34-38, and a composition comprising an IL-16 antagonist and a pharmaceutically acceptable carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 1-33, 35, and 40-41 at pg 5-7 of the previous Office Action (Paper No. 16, 15 August 2001).

Claims 1-33 and 35 are directed to an isolated IL-16 antagonist peptide consisting of a sequence selected from the group consisting of SEQ ID NOs: 2-7, 9-11, 13-32, and 34-38 and a pharmaceutical composition comprising the IL-16 antagonist peptide and a pharmaceutically acceptable carrier. The claims also recite an isolated nucleic acid molecule coding for an IL-16 antagonist peptide. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of the enabling disclosure.

Applicant's arguments (Paper No. 17, 15 March 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the specification teaches that all the claimed peptides share certain structural characteristics. Applicant contends that the specification teaches that an IL-16 antagonist peptide of the present invention corresponds to the C-terminal sequence of an IL-16 protein surrounding the Arg/Lys-Arg motif. Applicant indicates that the claimed peptides all contain the Arg/Lys-Arg motif and substantially correspond to the C-terminal sequence of a naturally occurring IL-16 molecule. Applicant argues that the IL-16 antagonist peptides of the present invention share common structural characteristics. Applicant also states that the specification teaches these shared structural characteristics are attributed to the function of the these peptides. Applicant cites pg 37 of the specification to emphasize that the specification discloses that in an IL-16 antagonist peptide, the replacement of the first Arg residue in the Arg/Arg motif with Ala, or the replacement with both Arg residues with Ala, completely abrogates the antagonist property of the peptide. Applicant indicates that substitutions of residues adjacent to the Arg/Arg motid often do not affect the antagonist activity of the peptide. Additionally, Applicant argues that based upon the exemplification of the antagonistic activities of IL-16 antagonist peptides of SEQ ID NOs: 2, 5, 6, 17, and 24, the skilled artisan would readily appreciate that peptides of SEQ ID NOs: 3-4, 9-11, 13-16, 18-23, 25-32, and 34-38 have biological activities similar to the antagonist peptides of SEQ ID NOs: 2, 5, 6, 17, and 24. Applicant provides the results of experiments using the peptides of SEQ ID NOs: 24 and 26 as Exhibit A.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification teaches working examples to demonstrate that the isolated antagonist peptides of SEQ ID NOs: 2, 5, 6, 17, and 24 inhibit IL-16 stimulated human T lymphocyte cell migration (pg 34-35). However, the specification does not teach any methods or working examples to demonstrate that the isolated peptides of SEQ ID NOs: 3-4, 9-11, 13-16, 18-23, 25-32, and 34-38 are capable of inhibiting IL-16 mediated T lymphocyte migration. As discussed in the previous Office Action (Paper No. 16, 15 August 2001), the assumption that the peptides of SEQ ID NOs: 3-4, 9-11, 13-16, 18-23, 25-32, and 34-38 have biological activities similar to the antagonist peptides of SEQ ID NOs: 2, 5, 6, 17, and 24 cannot be accepted in the absence of supporting evidence because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has

provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions, additions, or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Although Applicant indicates Exhibit A details *in vitro* results utilizing the IL-16 antagonistic peptides of SEQ ID NO: 26, Applicant's argument is not persuasive because the evidence in the Exhibit must be submitted in the form of a declaration under 37 C.F.R. 1.132. Exhibit A is not proper evidence, since its contents have not been peer-reviewed or have not been attested to under 37 CFR 1.132. Without submission under 37 C.F.R. 1.132 , it is unclear where the data in the specification and the Exhibit originate from. However, if submitted under 37 C.F.R. 1.132, the results in the Exhibit would be persuasive *in part*. Since the IL-16 antagonist peptide of SEQ ID NO: 26 inhibits IL-16 stimulated human T lymphocyte cell migration, the specification would be enabling for an isolated IL-16 antagonist peptide consisting of the amino acid sequence of SEQ ID NOs: 2, 5, 6, 17, 24, and 26 and a composition

comprising an isolated IL-16 antagonist peptide consisting of the amino acid sequence of SEQ ID NOs: 2, 5, 6, 17, 24, and 26 and a carrier.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to screen the numerous peptide sequences recited in the claims for antagonistic activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of mutation on protein structure and function (see discussion and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth for claims 35 and 41 at pg 7-8 of the previous Office Action (Paper No. 16, 15 August 2001).

Claims 35 is directed to a pharmaceutical composition comprising an isolated IL-16 antagonist peptide and a pharmaceutically acceptable carrier.

Applicant's arguments (Paper No. 17, 15 March 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the specification of the instant application provides adequate teaching as to how to use the claimed pharmaceutical compositions. Applicant argues that the

pharmaceutical compositions can be employed for the treatment of IL-16 mediated pathological disorders. Applicant contends that the specification also provides general guidelines for the therapeutic effective dosages of an IL-16 antagonist peptide as well as guidance as to the routes of administration. Applicant states that those skilled in the art may conduct additional experimentation to optimize the dosage and route of administration, but such additional experimentation is routine to those skilled in the art. Additionally, as support of enablement of the specification, Applicant also provides results of the therapeutic effects of the peptides of SEQ ID NOs: 24 and 33 on antigen-induced early and late airway responses, airway hyperresponsiveness and airway inflammation in allergic sheep in Exhibit B.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the word "pharmaceutical" is interpreted as the intended use of the composition, and thus the specification has to be examined with respect to the sole intended use. The specification does not teach any working examples that demonstrate administration of any IL-16 antagonist peptide to any animal for the treatment of any disorder or disease, particularly an IL-16 mediated pathological disorder. The section of the specification that Applicant refers to in the above arguments (pg 26-28) teaches a prophetic example of the formulation and administration of a "pharmaceutical" preparation of any IL-16 antagonist peptide. A prophetic example is not a working example. One skilled in the art would not know how to use the invention of the instant application because the invention is highly complex and a large quantity of experimentation is necessary to determine the proper dosage, route of administration, and appropriate patient population for any "pharmaceutical" composition, especially an IL-16 antagonist peptide. In the instant case, there is a low guidance level in the specification and an absence of working

examples. Additionally, the effects of the administration of a "pharmaceutical" composition comprising any IL-16 antagonist peptide are unpredictable in subjects. For example, are there any physical side effects? Do any of the claimed IL-16 antagonist peptides actually treat an IL-16 mediated pathological disorder?

Furthermore, the evidence in Exhibit B must be submitted in the form of a declaration under 37 C.F.R. 1.132. Exhibit B is not proper evidence, since its contents have not been peer-reviewed or have not been attested to under 37 CFR 1.132. Without submission under 37 C.F.R. 1.132 , it is unclear where the data in the specification and the Exhibit originate from. However, if submitted under 37 C.F.R. 1.132, the results in the Exhibits would not be persuasive. Although the results in Exhibit B indicate an 8-mer peptide and 16-mer peptide inhibit antigen-induced late phase airway resistance and hyperresponsiveness (asthma) in sheep, it cannot be determined in the "experimental protocol", "figure legends", and "figures" sections which claimed 8-mer and 16-mer peptides (ie, SEQ ID NOs: 24-32 and 34-38, respectively) are the ones utilized in the experiments. Applicant's response of 15 March 2002 (Paper No. 17) indicates the 8-mer peptide to be SEQ ID NO: 24 and the 16-mer peptide to be SEQ ID NO: 33 (see pg 12). It is noted that the peptide consisting of the sequence of SEQ ID NO: 33 is not claimed in the instant application and therefore, the assumption that other 16-mer peptides of SEQ ID NOs: 34-38 would have biological activities similar to the antagonist peptide of SEQ ID NO: 33 cannot be accepted in the absence of supporting evidence. As discussed in the previous Office Action (Paper No. 16, 15 August 2002) and elaborated upon above, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites

or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine the quantity of IL-16 antagonist peptide to be administered, the most effective administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the IL-16 antagonist peptide *in vivo,* undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

8. Claims 1-33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Regarding claims 1-33 and 35, the acronym and abbreviations "IL-16, Arg, Lys, Thr, Ala, Ser, Ile, Val, Leu" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity. The basis for this rejection is set forth at pg 9 of the previous Office Action (Paper No. 16, 15 August 2001).

Applicant's arguments (Paper No. 17, 15 March 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that the meanings of the terms "IL-16", "Arg", "Lys", "Thr", "Ala", "Ser", "Ile", "Val", and "Leu" are clear to those skilled in the art.

Applicant's arguments have been fully considered but are not found to be persuasive.

Specifically, abbreviations are less clear then the actual terms being abbreviated.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
May 31, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER